The Regioselectivity of Cycloaddition Reactions Between Diazomethane and 3-Vinylcephalosporins

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Diphenylmethyl (6*R*,7*R*)-7-phenylacetamido-3-vinylceph-3-em-4-carboxylate **1** undergoes regioselective addition of diazomethane to give the 1-pyrazoline **7**, which readily undergoes thermolysis to give the cyclopropyl analogue **10**. The regioselectivity is reversed, however, when one or more electron withdrawing ester substituents are attached to the 3-vinyl group.

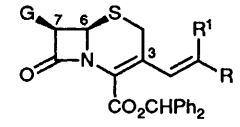
β-Lactams containing either *endo*- or *exo*-cyclic double bonds have been shown to undergo 1,3-dipolar cycloaddition with diazomethane. Thus the cephalosporin [1] and the carbapenem [2,3] nuclei have been shown to give pyrazolines, but only in one case [2] has the fused cyclopropyl derivative been observed during thermolysis. Similarly spirocyclopropyl analogues have been prepared from exomethylene cephalosporins *via* either their pyrazoline intermediates,[4,5] or using (dimethylamino)methylphenyloxosulphonium fluoroborate [6] directly as a cyclopropanylating reagent.

Recently, cyclopropyl substituents have been introduced directly into the cephalosporin system using diazomethane by a $Pd(OAc)_2$ catalysed insertion reaction,[7,8] as well as *via* the usual 1-pyrazoline intermediate.[9]

An investigation into novel cephalosporin antibiotics led us to prepare compounds having mono- or di-substituted cyclopropyl substituents in the 3-position. Cephalosporins bearing a vinyl group in this position have given rise to highly bioactive molecules such as cefixime [10] and FK 482 (cefdinir).[11] It was subsequently shown that the isosteric cyclopropyl group in **10** did not have the necessary electronic requirements to provide the potent antibacterial activity conferred by the vinyl group. By selecting cyclopropyl groups bearing electron withdrawing groups we expected that these requirements, and hence the activity, might be maintained.

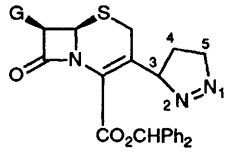
The 3-vinyl compound **1** was found to react with diazomethane in ether–dichloromethane at room temperature. The 1-pyrazoline product from this reaction was shown to be the regioisomer **7**,† by a combination of ^1H NMR, ^{13}C and 2D-COSY decoupling experiments. Thermolysis of **7** in refluxing ethyl acetate gave the 3-cyclopropyl cephalosporin **10**.

Having established this reaction, we then prepared representative examples of substituted vinyl analogues bearing various electron withdrawing groups. The styryl analogue **2** was readily obtained by reaction of the phosphorane **14**[10] derived *in situ* from the readily available chloride **12**‡ *via* the phosphonium salt **13**, with benzaldehyde. Although predominantly *cis*-, 10% of the inseparable *trans*-isomer is formed. In contrast, the 4-methylthiazol-5-yl derivative **3**, prepared from **14** in a Wittig condensation with the aldehyde **16**, gave predominantly the *trans*-isomer containing *ca.* 10% of the *cis*-product. The *trans*-methoxycarbonyl compound **4** was more readily prepared by reaction of methoxycarbonylmethylenetriphenylphosphorane with the 3-carbaldehyde **15**, and contained *ca.* 8–9% of the *cis*-isomer. Treatment of the phenyl analogue **2** and the thiazole compound **3** with diazomethane at room temperature resulted in recovery of starting material in both cases. A more polar product was observed in the case of the vinyl ester **4**. Characterization of this product by ^1H NMR spectroscopy demonstrated that the direction of 1,3-dipolar cycloaddition in this case was reversed, and that simultaneous isomerization of the N=N double bond gives the more stable α,β-unsaturated ester **8**.† The spectrum showed a clear ABX system with δ values for the AB sub-spectrum at 3.49 and 3.93, and X at 4.68. For a cycloaddition mechanism giving either of the possible structures **17** or **19** a different (more complex) coupling system would have been expected. Structure **18** was discounted on the observation of only one exchangeable NH signal at δ 6.22. By replacing the proton α to the substrate ester group, rearrangement would be prevented and hence the integrity of the 1-pyrazoline would be maintained. Unfortunately, the methyl analogue **5** was not obtained by reaction of **15** with 1-methoxycarbonylethylidenetriphenylphosporane, and reaction of **14** with methyl pyruvate led to a complex mixture of products. However, the bisester **6** was readily prepared from diethyl ketomalonate and **14**. The alkene **6** reacted with diazomethane to give the 1-pyrazoline **9** as a mixture of



G = $PhCH_2CONH$

1 $R^1 = R = H$
2 $R^1 = Ph$, $R = H$
3 $R^1 = H$, R = 
4 $R^1 = H$, $R = CO_2Me$
5 $R^1 = Me$, $R = CO_2Me$
6 $R^1 = R = CO_2Et$



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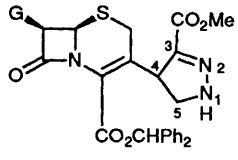

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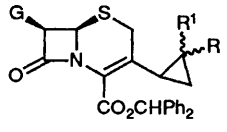
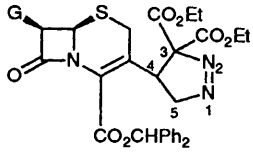


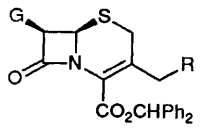
10 $R^1 = R = H$
11 $R^1 = R = CO_2Et$



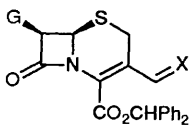
9a and b

† Compounds **7** and **8** were shown to be single diastereoisomers (^1H NMR), thus showing diastereoselectivity in the diazomethane cycloaddition

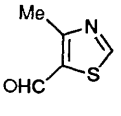
‡ Available from Otsuka Chemical Co. and used without further purification.



12 R = Cl
13 R = $\overset{+}{P}Ph_3\bar{I}$



14 X = PPh_3
15 X = O



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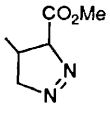

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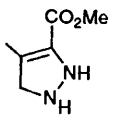

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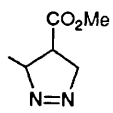

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diastereoisomers. Careful column chromatography allowed the isolation of small amounts of the more polar isomer **9b** as a single component. The less polar isomer **9a** was shown (^{1}H NMR, MS) to contain a small amount of an unknown component. Analysis of the spectrum of **9b** indicated non-equivalence in the protons of the ethyl ester groups, showing a complex set of AB quartets for the CH_2 protons. The presence of a single proton (δ 4.54, dd, J 8.0 and 18.3 Hz) and a more complicated two proton signal (δ 5.0, m) clearly demonstrated the regiochemical configuration of **9**. Thermolysis of **9b** in refluxing ethyl acetate resulted in nitrogen loss, but surprisingly an epimeric mixture of the corresponding cyclopropyl compounds **11** was obtained. Similar treatment of a mixture of **9a** and **9b** gave the same epimeric product mixture. We conclude that the methine proton of **9** and/or **11** is thermally labile.

The 3-cyclopropylcephalosporins substituted by one or two alkoxycarbonyl groups did not exhibit the potent level of antibacterial activity of the 3-vinyl series.

Experimental

UV spectra were recorded using a Perkin-Elmer 554 spectrophotometer. IR spectra were recorded for solutions in dichloromethane, using a Perkin-Elmer 197. ^{1}H NMR spectra were recorded at 250 or 400 MHz, on Bruker WM250 or WM400 instruments for solutions in $CDCl_3$ with tetramethylsilane as an internal standard. All J values are in Hz. Mass spectra were determined using an A.E.I. M59, a VG7070 or a VG ZAB instrument. 3-NOBA = 3-nitrobenzyl alcohol. The purity of all compounds was established by TLC analysis using Merck precoated silica gel $60F_{254}$ plates (0.2 mm thickness). Preparative chromatography was carried out on columns of silica gel 60 (finer than 230 mesh ASTM, Art 7729). 'Flash' chromatography refers to the practice of dry packing silica gel on short columns and drawing aliquots of solvent through under reduced pressure. During work-up, solutions were dried over anhydrous magnesium sulphate.

Diphenylmethyl (6R,7R)-7-*Phenylacetamido*-3-(1-*pyrazolin*-3-*yl*)*ceph*-3-*em*-4-*carboxylate* **7**.—Diphenylmethyl (6*R*,7*R*)-7-phenylacetamido-3-vinylceph-3-em-4-carboxylate[10] (3.78 g) dissolved in a minimum amount of dichloromethane was treated with an ethereal solution of diazomethane (containing *ca.* 0.93 g, 3 mol equiv.) at room temperature. After 3–4 h, TLC analysis (50% ethyl acetate–hexane) showed only trace amounts of starting material. Removal of the excess of diazomethane and solvent afforded a gum. Flash chromatography on silica gel eluting with 40 and then 50% ethyl acetate–hexane gave the cephem **7** as a pale yellow foam (2.296 g, 56%); ν_{max}/cm^{-1} 3400, 1785, 1720, 1680, 1490 and 1365; δ_H(400 MHz) 1.12 (1 H, m, pyrazoline 4-H), 2.12 (1 H, m, pyrazoline 4-H), 2.65 and 3.58 (2 H, ABq, J 18.6, SCH_2), 3.61 and 3.68 (2 H, ABq, J 16.2, CH_2Ph), 4.05 (1 H, m, pyrazoline 5-H), 4.81 (1 H, ddt, J 9.8, 17.6 and 2.4, pyrazoline 5-H), 5.07 (1 H, d, J 4.9, 6-H), 5.31 (1 H, br t, J 9.4, pyrazoline 3-H), 5.91 (1 H, dd, J 4.9 and 9.1, 7-H), 6.05 (1 H, d, J 9.1, CONH), 6.89 (1 H, s, C*H*Ph_2) and 7.24–7.41 (15 H, m, aromatic).

Diphenylmethyl (6R,7R)-3-*Cyclopropyl*-7-*phenylacetamido*-*ceph*-3-*em*-4-*carboxylate* **10**.—The pyrazoline **7** (0.1 g) in ethyl acetate (15 cm^3) was heated under reflux for *ca.* 48 h. The solvent was removed and the residual gum flash chromatographed on silica gel eluting with 30% ethyl acetate–hexane. The 3-*cyclopropyl compound* **10** was obtained as a colourless crystalline solid (0.06 g, 63%), m.p. 168–169 °C (ethyl acetate–hexane) (Found: M$^+$, 524.1778. $C_{13}H_{28}N_2O_4S$ requires M, 524.1770); ν_{max}/cm^{-1} 3400, 3300br, 1780, 1715, 1685 and 1595; δ_H(250 MHz) 0.40 (1 H, m, cyclopropyl 2-H), 0.50 (1 H, m, cyclopropyl 3-H), 0.76 (2 H, m, cyclopropyl 2,3-H), 2.37 and 2.73 (2 H, ABq, J 16.3, SCH_2), 2.68 (1 H, m, cyclopropyl 1-H), 3.63 and 3.70 (2 H, ABq, J 16.3, CH_2Ph), 4.96 (1 H, d, J 4.3, 6-H), 5.60 (1 H, dd, J 4.3 and 8.7, 7-H), 6.64 (1 H, d, J 8.7, CONH), 6.90 (1 H, s, C*H*Ph_2) and 7.23–7.45 (15 H, m, aromatic).

Diphenylmethyl (6R,7R)-7-*Phenylacetamido*-3-[(Z)-2-*phenylvinyl*]*ceph*-3-*em*-4-*carboxylate* **2**.—The phosphonium salt **13**[10] (3 g) was dissolved in dichloromethane (30 cm^3) and stirred vigorously with 10% aqueous sodium carbonate (20 cm^3) for 2 h. TLC analysis (10% methanol–ethyl acetate) showed loss of salt, with formation of the more polar phosphorane. The organic phase was separated, washed with brine and dried. After concentration to 10–15 cm^3, 5% aqueous sodium hydrogen carbonate (15 cm^3) and benzaldehyde (0.718 g) were added. The mixture was stirred vigorously for 8 h at room temperature. Again the organic phase was separated and washed successively with dilute hydrochloric acid and brine and then dried. Following removal of solvent under reduced pressure, the residue was purified by flash chromatography on silica gel eluting with 20, 30 and then 40% ethyl acetate–hexane. The product **2** was obtained as a pale yellow foam (0.576 g, 29%); ν_{max}/cm^{-1} 1780, 1715 and 1680; δ_H(250 MHz) 3.16 and 3.26 (2 H, ABq, J 18.3, SCH_2), 3.62 and 3.69 (2 H, ABq, J 16.2, CH_2Ph), 4.98 (1 H, d, J 4.8, 6-H), 5.85 (1 H, dd, J 4.8, 8.9, 7-H), 6.17 (1 H, d, J 8.9, CONH), 6.46 (1 H, d, J 12.0, CH=C), 6.62 (1 H, d, J 12.0, C=CH), 6.94 (1 H, s, C*H*Ph_2) and 7.12–7.54 (15 H, m, aromatic); *E*-isomer estimated at *ca.* 10% by integration of characteristic signals, *inter alia* δ 5.04 (1 H, d, J 4.8, 6-H), 5.63 (1 H, dd, J 4.8, 9.01, 7-H), 6.73 (1 H, d, J 16.4, CH=C) and 6.75 (1 H, s, C*H*Ph_2); m/z (FAB; 3-NOBA/Na) 609 (100%; MNa$^+$).

Diphenylmethyl (6R,7R)-3-[(E)-2-(4-*Methyl*-1,3-*thiazol*-5-*yl*)*vinyl*]-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* **3**.—The phosphorane **14** was generated from **13** (4.5 g) with 10% aqueous sodium carbonate (20 cm^3) in dichloromethane (30 cm^3) as described for compound **2**. To a solution of the phosphorane was added aqueous sodium hydrogen carbonate (1 mol dm^{-3}; 20 cm^3) and 4-methyl-1,3-thiazole-5-carbaldehyde **16**.[12] The solution was stirred vigorously for *ca.* 24 h. The organic layer was separated, washed with water and brine and then dried. Concentration and flash chromatography on silica gel, eluting with 50% ethyl acetate–hexane and then repeat chromatography with 80% ethyl acetate–hexane gave the cephem **3** as a yellow foam (0.496 g, 16%); ν_{max}/cm^{-1} 1780, 1705 and 1680; δ_H(250 MHz) 2.45 (3 H, s, Me), 3.36 and 3.54 (2 H, ABq, J 6.7, SCH_2), 3.64 and 3.70 (2 H, ABq, J 15.9, CH_2Ph), 5.11 (1 H, d, J 4.6, 6-H), 5.78 (1 H, dd, J 4.6, 8.9, 7-H), 6.63 (1 H, d, J 8.9, CONH), 6.72 (1 H, d, J 16.0, CH=C), 6.95 (1 H, s, C*H*Ph_2), 7.20–7.49 (16 H, m, aromatic and C=CH) and

8.51 (1 H, s, thiazole-H); *Z*-isomer estimated at 10% by integration with characteristic signals, *inter alia* δ 2.36 (1 H, s, Me), 3.21 and 3.48 (2 H, ABq, *J* 16.2, SCH_2), 5.08 (1 H, d, *J* 4.8, 6-H), 5.93 (1 H, dd, *J* 4.8 and 9.1, 7-H), 6.17 (1 H, d, *J* 9.1, CONH), 6.24 (1 H, d, *J* 11.8, CH=C), 6.49 (1 H, d, *J* 11.8, C=CH), 6.86 (1 H, s, C*H*Ph_2) and 8.56 (1 H, s, thiazole-H); *m/z* (FAB; 3-NOBA/Na) 608 (10%; MH^+) and 630 (32%; MNa^+).

Diphenylmethyl (6R,7R)-3-[(E)-2-*Methoxycarbonylvinyl*]-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* **4**.—The 3-formylcephem **15**,[13] (0.5 g) in dichloromethane (10 cm^3) was treated with a solution of methoxycarbonylmethylenetriphenylphosphorane (0.326 g) in dichloromethane (5 cm^3) in a dropwise fashion during 20 min, with stirring at room temperature for a further 40–50 min. TLC analysis (50% ethyl acetate–hexane) showed completion of the reaction. The solution was washed with aqueous hydrochloric acid (2 mol dm^{-3}, 10 cm^3) and then dried and concentrated. Purification by flash chromatography on silica gel eluting with 30, 40 and 50% ethyl acetate–hexane afforded **4** as a pale yellow foam (0.247 g, 44%); ν_{max}/cm^{-1} 1785, 1720 and 1690sh; δ_H(250 MHz) 3.44 and 3.55 (2 H, ABq, *J* 17.9, SCH_2), 3.59–3.66 (2 H, ABq, *J* 15.9, CH_2Ph), 3.73 (3 H, s, Me), 4.98 (1 H, d, *J* 5.1, 6-H), 5.90 (1 H, dd, *J* 5.1 and 9.1, 7-H), 6.00 (1 H, d, *J* 16.0, CH=C), 6.25 (1 H, d, *J* 9.1, CONH), 6.95 (1 H, s, C*H*Ph_2), 7.24–7.45 (15 H, m, aromatic) and 7.87 (1 H, d, *J* 16.0, –CH=); *Z*-isomer estimated at *ca.* 8–9% by integration, with characteristic signals at, *inter alia* δ 5.04 (1 H, d, *J* 4.9, 6-H), 5.70 (1 H, d, *J* 11.8, CH=C), 6.83 (1 H, s, C*H*Ph_2) and 6.87 (1 H, d, *J* 11.8, C=CH); *m/z* (FAB; 3-NOBA/Na) 591 (16%; MNa^+).

Reaction of 3-*Vinylcephems* **2–4** *with Diazomethane: Diphenylmethyl* (6R,7R)-3-[(4RS)-3-*Methoxycarbonyl*-2-*pyrazolin*-4-*yl*]-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* **8**.—Each of the 3-vinylcephems **2–4** (0.18 g) in dichloromethane (10 cm^3) was treated with an excess of ethereal diazomethane as described for the preparation of compound **7**. After 3 h at room temperature, TLC analysis (60% ethyl acetate–hexane) showed only the ester **4** had reacted. Compounds **2** and **3** were left for a further 2–3 d; no reaction was observed. In the case of **4**, the excess of diazomethane and solvent were removed under reduced pressure. Trituration with diethyl ether afforded the 2-pyrazoline **8** as an amorphous, buff-coloured solid (0.189 g, 97%); ν_{max}(KBr)/cm^{-1} 1780, 1707, 1658 and 1624; δ_H(250 MHz) 3.18 and 3.38 (2 H, ABq, *J* 18.2, SCH_2), 3.49 (1 H, dd, *J* 6.6, 10.8, pyrazoline 5-H), 3.60 and 3.69 (2 H, ABq, *J* 16.3, CH_2Ph), 3.78 (3 H, s, Me), 3.93 (1 H, dd, *J* 10.8 and 12.6, pyrazoline 5-H), 4.68 (1 H, dd, *J* 6.6 and 12.6, pyrazoline 4-H), 4.98 (1 H, d, *J* 4.7, 6-H), 5.86 (1 H, dd, *J* 4.7 and 9.1, 7-H), 6.02 (1 H, d, *J* 9.1, CONH), 6.22 (1 H, br s, exchangeable in D_2O, NH–N), 6.87 (1 H, s, $CHPh_2$) and 7.25–7.43 (15 H, m, aromatic); *m/z* (FAB; thioglycerol) 611 (12%; MH^+) and 633 (9%; MNa^+).

Diphenylmethyl (6R,7R)-3-[2,2-*Bis*(*ethoxycarbonyl*)*vinyl*]-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* **6**.—The phosphorane **14** (0.1 g) as a suspension in dry dichloromethane (1 cm^3) was treated with diethyl ketomalonate (0.069 g) at room temperature. After 1 h, TLC (40% ethyl acetate–hexane) showed a mobile product. The solution was concentrated and flash chromatographed on silica gel, eluting with 40% ethyl acetate–hexane to give a pale yellow foam. Trituration with methanol afforded *triester* **6** as a colourless crystalline solid (0.017 g, 82%), m.p. (ethyl acetate–hexane) 171–172 °C (decomp.) (Found: C, 66.29; H, 5.12; N, 4.34; S, 4.91. $C_{36}H_{34}N_2O_8S$ requires C, 66.04; H, 5.23; N, 4.28; S, 4.90%); ν_{max}/cm^{-1} 1785, 1720 and 1690sh; δ_H(250 MHz) 1.23 (3 H, t, *J* 7.2, Me), 1.25 (3 H, t, *J* 7.2, Me), 3.39 and 3.54 (2 H, ABq, *J* 18.1, SCH_2), 3.60 and 3.68 (2 H, ABq, *J* 16.2, CH_2Ph), 4.19 (2 H, q, *J* 7.2, CO_2CH_2Me), 4.23 (2 H, q, *J* 7.2, CO_2CH_2Me), 4.98 (1 H, d, *J* 4.0, 6-H), 5.88 (1 H, dd, *J* 4.0 and 9.0, 7-H), 6.08 (1 H, d, *J* 9.0, CONH), 6.94 (1 H, s, C*H*Ph_2), 7.25–7.44 (15 H, m, aromatic) and 7.68 (1 H, s, CH=C); *m/z* (FAB; 3-NOBA/Na) 677 (4%; MNa^+).

Diphenylmethyl (6R,7R)-3-[(4RS)-3,3-*Bis*(*ethoxycarbonyl*)-1-*pyrazolin*-4-*yl*]-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* **9a** *and* **b**.—The diester **6** (0.3 g) in dichloromethane (20 cm^3) was treated with an excess of ethereal diazomethane as described for compound **7**. TLC analysis showed formation of two, very close-running products. Subsequent work-up and purification by flash chromatography on silica gel, eluting with 40% ethyl acetate–hexane, afforded the pyrazoline **9** as a mixture of diastereoisomers **a** and **b**, as a pale yellow foam (0.316 g, 99%). Repeated column chromatography allowed the isolation of small amounts of pure isomers. The first isomer eluted was **9a** ν_{max}/cm^{-1} 3413, 1788, 1738 and 1689; δ_H(250 MHz) 1.18 (3 H, t, *J* 7.1, Me), 1.25 (3 H, t, *J* 7.1, Me), 2.48 and 2.77 (2 H, ABq, *J* 17.9, SCH_2), 3.60 and 3.68 (2 H, ABq, 16.3, CH_2Ph), 4.02–4.34 (4 H, m, 2 × CO_2CH_2Me), 4.58 (1 H, dd, *J* 18.4 and 7.9, pyrazoline 4-H), 4.80–4.88 (3 H, m, pyrazoline 5-H_2 and β-lactam 6-H), 5.78 (1 H, dd, *J* 9.0 and 4.0, 7-H), 5.93 (1 H, d, *J* 9.0, CONH), 6.96 (1 H, s, C*H*Ph_2) and 7.23–7.44 (15 H, m, aromatic); *m/z* (FAB; NOBA/Na) 851 (32%; MNa^+).

The second isomer eluted was **9b** ν_{max}/cm^{-1} 3411, 1789, 1736 and 1689; δ_H(250 MHz) 1.04 (3 H, t, *J* 7.1, Me), 1.27 (3 H, t, *J* 7.1, Me), 2.51 and 2.89 (2 H, ABq, *J* 17.0, SCH_2), 3.61 and 3.68 (2 H, ABq, *J* 16.3, CH_2Ph), 3.97–4.34 (4 H, m, 2 × CO_2CH_2Me), 4.54 (1 H, dd, *J* 18.3 and 8.0, pyrazoline 4-H), 4.83–5.13 (3 H, d, *J* 4.8, 6-H overlapping m, pyrazoline 5-H_2), 5.73 (1 H, dd, *J* 8.7 and 4.8, 7-H), 5.93 (1 H, d, *J* 8.7, CONH), 6.99 (1 H, s, C*H*Ph_2) and 7.25–7.43 (15 H, m, aromatic; *m/z* (FAB; 3-NOBA/Na) 719 (18%; MNa^+).

Diphenylmethyl (6R,7R)-3-[(1RS)-2,2-*Bis*(*ethoxycarbonyl*)-*cyclopropyl*]-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* **11**.—(*a*) A diastereoisomeric mixture of pyrazolines **9a** and **b** (0.183 g) in ethyl acetate was heated under reflux for 48 h. TLC analysis (50% ethyl acetate–hexane) showed only a single component. The solvent was removed under vacuum and the residual gum flash chromatographed on silica gel eluting with 40% ethyl acetate–hexane. The cyclopropyl compound **11** was obtained as a colourless foam (0.15 g, 87%), as a diastereoisomeric mixture, ν_{max}/cm^{-1} 1788, 1728 and 1691; δ_H(250 MHz) 1.12 (3 H, t, *J* 7.0, Me), 1.27 (5 H, t, *J* 7.0, Me overlapping m, cyclopropyl 3-H_2), 3.05–3.24 (1 H, m, SCH), 3.52–3.24 (2 H, m, SCH overlapping cyclopropyl 1-H), 4.97 and 5.03 (1 H, 2 × d, *J* 4.7, 6-H), 5.82 and 5.88 (1 H, 2 × dd, *J* 4.7, 9.1, 7-H), 6.88 and 6.97 (1 H, 2 × s, C*H*Ph_2) and 7.27–7.43 (15 H, m, aromatic); *m/z* (FAB; 3-NOBA/Na 691 (7%; MNa^+).

(*b*) The pure pyrazoline **9b** (0.1 g) in ethyl acetate (4 cm^3), was heated under reflux overnight to give, after work-up and purification, the cyclopropyl analogue **11** as a pale yellow foam (0.071 g, 74%). The ^1H NMR spectrum showed a 4:1 mixture of isomers.

Acknowledgements

We are grateful to Mr. J. W. Tyler and his colleagues for the NMR, IR and MS data and to Mr. G. Powell for microanalyses. We also thank Miss T. M. Bartlett for the typing.

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Paper 1/00339I
Received 23*rd January* 1991
Accepted 18*th February* 1991